

REMARKS

I. Status Summary

Claims 44, 47, 48, and 51-57 are pending in the current application and have been examined.

Claims 44, 47, 48, and 51-54, 56 and 57 have been rejected under the written description and/or enablement provisions of 35 U.S.C. § 112, first paragraph. The rejections include new matter rejections of claims 44, 53, and 54, and enablement rejections of all claims.

Claims 44, 47, 48, and 51-57 have been subjected to a series of rejections under 35 U.S.C. § 112, second paragraph, upon the contention that the claims are indefinite.

Claims 44, 47, 48, and 52-55 remain rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by Chang *et al.* (1995, *Cell Biol. Intl*, Vol 19, pg. 143-149; hereinafter "Chang 1995") or by Chang *et al.* (1997, *Cell Biol Intl*, 21:495-499; hereinafter "Chang 1997").

Claims 44, 47, 48, and 51-57 have been rejected under 35 U.S.C. § 102(e) upon the contention the claims are anticipated by U.S. Patent No. 5,340,740 (hereinafter "the '740 Patent"); U.S. Patent No. 5,656,479 (hereinafter "the '479 Patent"); or U.S. Patent No. 5,840,510 (hereinafter "the '510 Patent").

Claims 44, 47, 48, and 51-57 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are obvious over U.S. Patent No. 6,156,569 (hereinafter "the '569 Patent") in view of Chang 1995.

Claims 44, 47, 48, and 51-57 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 8-10 of the '740 Patent, claim 1 of the '479 Patent or the '510 Patent, or claims 1-12 of the '659 Patent, each in view of Chang 1995.

Claim 55 has been canceled. Claims 44, 47, and 48 have been amended. Support for the amendments can be found throughout the specification of the application as filed, including particularly at page 9, lines 5-6. Additional support for the amendments can be found on page 4, lines 18-20, and on page 21, lines 9-10.

New claim 58 has been added. Support for the new claims can be found throughout the specification of the application as filed, including particularly in Figure 4.

No new matter has been added by virtue of the claim amendments or the addition of the new claims. Reconsideration of the application as amended and based on the remarks set forth below is respectfully requested.

II. Summary of Telephone Interview Conducted August 2, 2005

A telephone interview was conducted on August 2, 2005. Participating in the interview were Examiner Michael C. Wilson of the United States Patent and Trademark Office (hereinafter "the Patent Office") and applicants' representatives Arles A. Taylor, Jr. and Christopher P. Perkins. Discussed during the interview were the pending rejections of the claims under 35 U.S.C. § 112, first and second paragraphs, and under 35 U.S.C. §§ 102 and 103. Applicants' representatives would like to thank Examiner Wilson for his time and efforts in participating in the telephone interview.

In particular, Examiner Wilson and applicants' representatives discussed the phrase "expressing an embryonic stem cell phenotype". No agreements were reached.

The claims were also discussed in view of the Chang 1995 and Chang 1997 references. No agreements were reached.

III. Responses to the Rejections under 35 U.S.C. § 112, First Paragraph

Claims 44, 53, and 54 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. According to the Patent Office, the specification does not contemplate maintaining an ES cell phenotype for one or two months as recited in claims 53 and 54, and the phrase "one or more colonies" recited in claim 44 is new matter.

After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

III.A. Response to the New Matter Rejection of Claims 53 and 54

The new matter rejection of claims 53 and 54 has been maintained from the previous Official Action. In response to that Official Action, applicants argued that page 13, line 21, through page 14, line 7, of the specification disclosed a sustained culture of undifferentiated avian cells expressing an embryonic stem cell phenotype wherein the embryonic stem cell phenotype is maintained for at least one or two months. This section of the specification is presented below:

In a preferred embodiment, avian embryonic gonadal cells comprising primordial germ cells from a four to five day incubated avian embryo are seeded onto the preconditioned feeder matrix with conditioned media, and the avian cells give rise to nests or colonies of cells exhibiting an embryonic stem cell phenotype. Unlike the case with mammalian stem cells, it is currently preferred to have a preconditioned feeder matrix to facilitate the survival and development of avian PGCs into undifferentiated avian cells expressing an ESC phenotype. The avian embryo cells of the present invention can be cultured for at least one or two months as is typical for a primary cell culture, which is significantly greater than the usual two week life of primary cultures of cells from an unincubated avian embryo.

Specification at page 13, line 21, to page 14, line 7. According to the Patent Office, this passage:

merely states that PGCs are maintained for one or two months. The specification did not teach or suggest that cells having an ES cell phenotype were maintained in culture for one or two months and does not explicitly or implicitly suggest that the ES cell phenotype is maintained for one or two months as claimed. The specification did not teach or suggest the ES cell phenotype was maintained in culture for one to two months as claimed.

Official Action at page 4.

Applicants respectfully disagree. Initially, applicants respectfully submit that the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement (66 Federal Register 1099, 2001; hereinafter the "Guidelines") specifically states "there is a 'strong presumption' that an adequate written description of the claims invention is present when the application is filed, consistent with *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976)" (emphasis

added). The Guidelines continue that “the burden of proof is on the examiner to establish that a description as filed is not adequate and require the examiner to introduce sufficient evidence or technical reasoning to shift the burden of going forward with contrary evidence to the applicant” (Guidelines at page 1100; emphasis added). Applicants respectfully submit that the Patent Office has not provided the required “sufficient evidence or technical reasoning”, and instead has only presented one potential interpretation of the passage cited hereinabove that is insufficient to overcome a strong presumption.

To elaborate, applicants respectfully submit that the presentation of an alternative interpretation of a portion of the specification is not sufficient to overcome a strong presumption of the adequacy of the written description. This point is also stated in the Guidelines, which states “The Guidelines indicate that for both original and amended claims, the inquiry is whether one skilled in the art can reasonably conclude that the inventor had possession of the invention at the time the application was filed” (Guidelines at page 1102; emphasis added). Applicants respectfully submit that even assuming *arguendo* that the Patent Office’s proffered interpretation is a reasonable interpretation, applicants’ proffered interpretation that the ES cell phenotype was maintained in culture for one to two months as claimed is also reasonable. Applicants further respectfully submit that the specification as a whole teaches the creation of sustained cultures of undifferentiated avian cells.

Accordingly, when the specification is considered as a whole, applicants respectfully submit that the disclosure is directed to the production of colonies of undifferentiated avian cells (*i.e.*, cells expressing an ESC phenotype). Thus, applicants respectfully submit that the only reasonable interpretation of the cited passage is that the cells in the culture after one month and after two months maintain the undifferentiated state (*i.e.*, the ESC phenotype).

Summarily, applicants respectfully submit that the Patent Office’s assertions do not overcome the strong presumption that the specification complies with the written description requirement of 35 U.S.C. § 112. As a result, applicants respectfully request

the withdrawal of the rejection with respect to 53 and 54, and the allowance of these claims at this time.

III.B. Response to the New Matter Rejection of Claim 44

Claims 44 has been rejected under the written description provision of the first paragraph of 35 U.S.C. § 112 upon the contention that the specification does not contemplate the lower limit of “one” colony inherent in the phrase “one or more colonies” recited in claim 44. Applicants respectfully traverse the instant rejection.

Initially, applicants respectfully submit that one of ordinary skill in the art would understand that under some culture conditions it is possible that only one colony of undifferentiated cells would arise. Thus, while it may be beneficial for more than one colony of such cells to be generated, it is reasonable to interpret the specification to disclose the generation of but one colony.

Furthermore, applicants respectfully submit that Figure 3A clearly discloses that under some culture conditions and at some time points, only one colony is present. With reference to Figure 3A, it is clear that there are four examples of conditions under which only one colony was present.

Accordingly, applicants respectfully submit that the skilled artisan would understand after consideration of the specification as filed that applicants had possession of a sustained culture containing one or more colonies as recited in claim 44. As a result, applicants respectfully submit that the recitation of “one or more colonies” is supported by the specification. Applicants respectfully request that the instant rejection be withdrawn, and that claim 44 be allowed at this time.

IV. Response to the Enablement Rejection

Claims 44, 47, 48, and 51-57 have been rejected under the enablement provision of 35 U.S.C. § 112, first paragraph, on two bases. The Patent Office asserts that while the specification is enabling for a culture comprising chicken ES cells, does not reasonably provide enablement for (i) a culture of avian ES cells other than chicken ES cells; and (ii) a culture wherein ES cells are maintained for one or two months.

After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

With respect to the first aspect of the instant rejection, claim 44 has been amended to recite chicken cells in order to facilitate prosecution of the instant claims. Applicants respectfully submit that this amendment is not to be construed as acquiescence that the Patent Office's assertions with regard to other avian species is correct. Applicants respectfully reserve the right to file one or more continuation applications with claims directed to the subject matter of claim 44 prior to the instant amendment. Nonetheless, applicants respectfully submit that the first aspect of the enablement rejection has been addressed by amending claim 44 to recite the embodiments that the Patent Office concedes are enabled.

Turning now to the second aspect of the instant rejection, applicants respectfully submit that the Patent Office appears to base this rejection on the assertion that the specification does not disclose that the ES cell phenotype is maintained for at least one or two months. Applicants direct the Patent Office's attention to the discussion hereinabove with respect to the corresponding written description rejection.

Applicants respectfully submit that the art cited by the Patent Office on pages 7 and 8 of the Official Action do not support the instant rejection. For example, the Simkiss, Petitte, and Ponce de Leon journal articles and the '569 Patent cited in the Official Action all relate to culture of PGCs, and not to a culture comprising one or more colonies of undifferentiated avian cells derived from PGCs as recited in the instant claims. Applicants respectfully submit that the culture conditions that are required to maintain PGCs in long-term culture do not inform the skilled artisan as to what culture conditions would be required to maintain colonies of undifferentiated avian cells derived from PGCs in long-term culture.

For example, applicants respectfully submit that the Ponce de Leon cultures do not employ feeder matrices (see Ponce de Leon at page 99; see *also* the '569 Patent at column 5, lines 48-49). Thus, the requirement for LIF, bFGF, IGF, and SCF in the Ponce de Leon culture system is not relevant to the instantly claimed culture system.

Applicants respectfully submit that the fact that the Ponce de Leon references disclose a requirement for LIF, bFGF, IGF, and SCF that provides long-term culture of PGCs is not relevant to the instant claims, because the instant claims are not directed to culture of PGCs. The sustained culture recited in the present claims includes a cell type that is not a PGC, but is derived from PGCs. Ponce de Leon and the '569 Patent teach long term culture of PGCs, while the instant application claims cultures including undifferentiated chicken cells that (i) are derived from chicken PGCs isolated from a later than Stage 14 embryo; (ii) are smaller than PGCs; and (iii) form one or more colonies of tightly packed undifferentiated chicken cells expressing an embryonic stem cell phenotype. Thus, the cell types being cultured are different, and the teaching of Ponce de Leon and the '569 Patent with respect to the culture of the claimed cells is believed to be inapplicable.

Summarily, applicants respectfully submit that the Patent Office's reliance on the state of the art as taught by the Simkiss, Petitte, and Ponce de Leon journal articles and the '569 Patent is improper as the culture conditions disclosed therein are irrelevant to the culture of the instantly claimed undifferentiated cells. As a result, applicants respectfully request that the rejection of claims 44, 47, 48, and 51-57 under 35 U.S.C. § 112, first paragraph, be withdrawn. Claim 55 has been canceled, and thus the rejection is believed to be moot as to this claim. Applicants respectfully submit that claims 44, 47, 48, 51-54, 56, and 57 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

V. Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 44, 47, 48, and 51-55 have been rejected on several bases under 35 U.S.C. § 112, second paragraph, upon the contention that certain terms and phrases appearing in the claims are unclear. Applicants have considered the individual rejections and the bases therefor, respectfully traverse the rejections, and submit the following remarks.

V.A. Response to the First Indefiniteness Rejection

The first basis for rejection rests on the Patent Office's assertion that the phrase "undifferentiated avian cells expressing an embryonic stem cell phenotype" is unclear (claim 44). According to the Patent Office, "it is unclear if the cells merely share a phenotype in common with avian ES cells or if the cells are avian ES cells". Official Action at page 11.

Applicants respectfully submit, and the Patent Office concedes, that the above-noted phrase is specifically defined in the specification. Applicants further respectfully submit that the phrase refers to cells with a certain morphology that those of skill in the embryonic stem cell art recognize as being characteristic of ES cells and ES-like cells: namely, a large nucleus, a prominent nucleolus, and little cytoplasm. See Specification at page 9, lines 5-6. This morphological characterization of the cells is conceded by the Patent Office to be known to the skilled artisan, and thus is not indefinite. Accordingly, applicants respectfully request that the instant rejection be withdrawn at this time.

To aid in the prosecution of the instant claims, however, applicants have amended claim 44 to recite *inter alia* that the undifferentiated chicken cells (i) are derived from the chicken primordial germ cells isolated from the chicken embryo; (ii) are smaller than the chicken primordial germ cells; and (iii) form one or more colonies of tightly packed undifferentiated chicken cells expressing an embryonic stem cell phenotype.

Thus, applicants respectfully submit that they have described the "embryonic stem cell phenotype" in such a way as to inform the skilled artisan as to the metes and bounds of the claims. As a result, applicants respectfully request that the instant rejection be withdrawn at this time.

V.B. Response to the Second Indefiniteness Rejection

The Patent Office next contends that the definition of "embryonic stem cell phenotype" is unclear because the phrase "refers to" on page 9, line 4, "makes the citation unclear because it cannot be determined if 'refers to' is intended to define the phenotype or merely to describing to what the phenotype is relevant". Official Action at page 8. The Patent Office continues to cite other passages from the specification that it

alleges renders the phrase unclear. However, applicants respectfully submit that the Patent Office has adopted an improper standard for measuring claim terminology under the second paragraph of § 112. The correct standard is not whether certain phrases taken from isolated sections of the specification can be interpreted in different ways, but whether the specification taken as a whole adequately informs the skilled artisan as to the metes and bounds of the claims.

Applicants respectfully submit that the specification clearly defines the meaning of the phrase “embryonic stem cell phenotype” to refer to cells that have a large nucleus, a prominent nucleolus, and little cytoplasm. Thus, the “embryonic stem cell phenotype” is a morphological description of the undifferentiated cells that applicants submit, and the Patent Office concedes, is an art-recognized description.

Notwithstanding the above and in an effort to facilitate prosecution of the instant claims, however, applicants have amended claim 44 to recite that the instantly claimed sustained culture comprises *inter alia* undifferentiated chicken cells that (i) are derived from the chicken primordial germ cells isolated from a later than Stage 14 chicken embryo; (ii) are smaller than the chicken primordial germ cells; and (iii) form one or more colonies of tightly packed undifferentiated chicken cells expressing an embryonic stem cell phenotype. These amendments are not to be construed as a surrender of any subject matter originally encompassed by the claim.

Thus, when the phrase at issue is viewed in the context of the specification taken as a whole as is required under the holding of Phillips V. AWH Corp., 415 F.3d 1303, 75 USPQ2d 1321, Fed. Cir. 2005 (“Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification”, 415 F. 3d at page 1313), applicants respectfully submit that one of ordinary skill in the art would understand the metes and bounds of the phrase “embryonic stem cell phenotype”. Accordingly, applicants respectfully submit that the instant aspect of the rejection under the second paragraph of § 112 has been addressed.

V.C. Response to the Third Indefiniteness Rejection

The Patent Office next asserts that it remains unclear how PGCs isolated from an embryo later than stage 14 are distinguished from PGCs isolated from a stage X or a stage 14 embryo. According to the Patent Office, PGCs isolated from stage X, 14, and after stage 14 have the same structure and function.

Applicants respectfully submit that the Patent Office contention that PGCs isolated from stage X, stage XIV, stage 14, or after stage 14 have the same structure and function has not been supported by competent scientific authority as is required for any statement for which the Patent Office takes official notice. Thus, the Patent Office's assertion that PGCs from these stages "have the same structure and function" lacks requisite support.

Additionally, applicants respectfully submit that the Patent Office's assertion is contrary to the understanding of those of skill in the art at the time of filing because prior to the disclosure in applicants' specification, it was not believed to be possible to provide a sustained culture of undifferentiated avian cells that could be derived from PGCs isolated from a later than stage 14 embryo. As such, applicants respectfully submit that those of skill in the art believed that PGCs did not have the same structure and function of PGCs isolated prior to this stage. Indeed, it was believed that PGCs isolated from later than stage 14 embryos had already initiated commitment to terminal differentiation into germ cells. Accordingly, the Patent Office's beliefs to the contrary are insufficient to support a rejection under § 112, second paragraph.

Applicants respectfully submit that the claim terminology itself is clear: chicken primordial germ cells and stromal cells isolated together from the embryonic genital ridge or gonad from a chicken embryo at a stage later than stage 14 according to the Hamburger & Hamilton staging system. Thus, given that the language of the claim itself is clear, applicants respectfully submit that the asserted basis for the instant rejection does not support a rejection under the second paragraph of § 112.

In summary, applicants respectfully submit that the rejections of claims 44, 47, 48, and 51-57 under 35 U.S.C. § 112, second paragraph, have been addressed, and that the claims are in condition for allowance at this time. Claim 55 has been canceled,

and thus the rejection is believed to be moot as to this claim. Applicants respectfully solicit a Notice of Allowance as to claims 44, 47, 48, and 51-54, 56, and 57.

VI. Rejections under 35 U.S.C. § 102

VI.A. Response to the Rejection in view of Chang 1995

Claims 44, 47, 48, and 52-55 have been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by Chang 1995. According to the Patent Office, Chang 1995 taught making feeder cells by isolating cells from the genital ridge of day 5 embryos and culturing the cells for 4 days. The Patent Office further asserts that the feeder cells are “preconditioned” because they are in culture for 4 days prior to the addition of day 2 PGCs, that the feeder cell media is “conditioned” because it contains biologically active components obtained from the previous 4 days in culture prior to adding day 2 PGCs, and that the cells isolated from the genital ridge comprised stromal cells and PGCs as claimed. Applicants have carefully considered the rejection and the Patent Office’s bases therefor, and respectfully traverse the rejection as follows.

Applicants respectfully submit that Chang 1995 does not support the instant rejection of the claims because Chang 1995 does not disclose each and every element of the claims. Specifically, Chang 1995 does not disclose the production of a sustained culture comprising undifferentiated chicken cells, wherein the undifferentiated chicken cells (i) are derived from chicken PGCs isolated from the genital ridge or gonad of a later than stage 14 embryo, (ii) are smaller than the chicken PGCs so isolated; and (iii) form one or more colonies of tightly packed undifferentiated chicken cells that express an embryonic stem cell phenotype. Rather, Chang 1995 discloses only PGC cultures, the cells of which are then transferred into chicken embryos where they colonize only the gonad of the recipient chicken.

Stated another way, Chang 1995 discloses removing PGCs, culturing them as PGCs in the short term, and returning them to a recipient where they colonize only the gonad. Since PGCs normally colonize the gonad, Chang 1995 does not disclose a change in either the phenotype or behavior of the isolated cells.

In contrast, claim 44 recites a sustained culture comprising *inter alia* one or more colonies of tightly packed undifferentiated cells that are derived from PGCs, each individual cell of which is smaller than a PGC. The cited Chang 1995 reference teaches a short-term culture of PGCs, not a culture that includes undifferentiated derivatives of PGCs that are smaller than PGCs and form tightly packed colonies.

Since Chang 1995 does not disclose each and every element of claim 44, applicants respectfully submit that Chang 1995 does not anticipate claim 44. Claims 47, 48, and 52-55 all depend directly or indirectly from claim 44, and thus include all the elements of distinguished claim 44. Accordingly, applicants respectfully request the withdrawal of the rejection of claims 44, 47, 48, and 52-55 in view of Chang 1995. Claim 55 has been canceled, and thus the rejection is believed to be moot as to this claim. Applicants respectfully request a Notice of Allowance for claims 44, 47, 48, and 52-54.

VI.B. Response to the Rejection in view of Chang 1997

Claims 44, 47, 48, and 52-55 have been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by Chang 1997. According to the Patent Office, Chang 1997 teaches isolating germinal ridge stromal cells from stage 27-28 embryos, which were then cultured for 5 days in media containing IGF, FGF, and LIF with germinal ridge stromal feeder cells isolated from day 5 embryos to obtain gPGCs. Applicants have carefully considered the rejection and the Patent Office's bases therefor, and respectfully traverse the rejection as follows.

Applicants respectfully submit that Chang 1997 does not anticipate the claims because the cited reference does not disclose every element of the claims for precisely the same reasons as outlined hereinabove with respect to Chang 1995. In particular, Chang 1997 does not teach a sustained culture comprising *inter alia* of PGC derivatives that comprises one or more tightly packed colonies of undifferentiated cells, each individual cell of which is smaller than a PGC.

Rather, Chang 1997 teaches the short-term (*i.e.*, 5 day) culture of chicken PGCs. Chang 1997 does not disclose that at 5 days, colonies of undifferentiated chicken cells are produced. This is clearly pointed out on page 496 of Chang 1997, wherein it is

states that “[a]fter 5 days in culture, the gPGCs landing on primary cultured GRSCs were suspended by gentle pipetting without using digestive enzymes”. Chang 1997 at page 496 (emphasis added). As one of ordinary skill in the art would recognize, gentle pipetting without the use of digestive enzymes would not release colonies of undifferentiated cells, which can require digestive enzymes to disrupt the colonies into their individual cells.

Thus, the cells disclosed in Chang 1997 are simply PGCs. Accordingly, like Chang 1995, Chang 1997 only discloses expanding PGC numbers in culture, and that when the PGCs are reintroduced into avian embryos they behave just like normal PGCs: they colonize the gonad. Stated another way, Chang 1997 teaches a method of culturing PGCs to produce an increased number of PGCs. This is unlike the sustained culture of claim 44, which comprises undifferentiated chicken cells, wherein the undifferentiated chicken cells (i) are derived from chicken PGCs isolated from the genital ridge or gonad of a later than stage 14 embryo, (ii) are smaller than the chicken PGCs so isolated; and (iii) form one or more colonies of tightly packed undifferentiated chicken cells that express an embryonic stem cell phenotype.

Since Chang 1997 does not disclose each and every element of claim 44, applicants respectfully submit that Chang 1997 does not anticipate claim 44. Claims 47, 48, and 52-55 all depend directly or indirectly from claim 44, and thus include all the elements of distinguished claim 44. Accordingly, applicants respectfully request the withdrawal of the rejection of claims 44, 47, 48, and 52-55 in view of Chang 1997. Claim 55 has been canceled, and thus the rejection is believed to be moot as to this claim. Applicants respectfully request a Notice of Allowance for claims 44, 47, 48, and 52-54.

VI.C. Response to the Rejection in view of the Petite Patents

Claims 44, 47, 48, and 52-55 have been rejected under 102(e) as being anticipated by U.S. Patent Nos. 5,340,740; 5,656,479; or 5,840,510 (hereinafter collectively referred to as “the Petite Patents”). According to the Patent Office, the Petite Patents teach culturing cells from a stage X embryo and isolating PGCs (‘740 Patent). The cells were seeded onto chicken embryonic fibroblast feeder layers and

cultured with BRL conditioned medium. The Patent Office asserts that “PGCs isolated from stage X are equivalent to PGCs isolated later than stage 14 as claimed because PGCs isolated from stage X and XIV have the same function”. See Official Action at page 19 (emphasis added). Applicants have carefully considered the rejection and the Patent Office’s bases therefor, and respectfully traverse the rejection as follows.

Applicants respectfully submit that the Petitte Patents do not disclose each and every element of the present claims. Specifically, the Petitte Patents do not disclose the use of PGCs isolated from the gonad or genital ridge of an avian embryo at a stage later than stage 14.

Applicants respectfully submit that the Patent Office’s assertion that the Petitte Patents disclose that “PGCs and stromal cells were inherently ‘isolated together from the embryonic genital ridge or gonad’ as claimed because the whole embryo was isolated and inherently contained both PGCs and stromal cells in the genital ridge or gonad” is inaccurate because stage X embryos have neither a genital ridge nor a gonad. The chicken embryo at Stage X (*i.e.*, a blastoderm stage) has not yet formed the three primary germ layers: ectoderm, mesoderm, and endoderm. Hence, the Patent Office’s assertion that there is a gonadal ridge or stromal cells in a Stage X embryo is inaccurate. Thus, applicants respectfully submit that one of ordinary skill in the art would understand that those structures are not present in the Stage X embryo. Accordingly, the Petitte patents cannot be read to disclose this element of claim 44.

Since the Petitte Patents do not disclose each and every element of claim 44, applicants respectfully submit that the Petitte Patents do not anticipate claim 44. Claims 47, 48, and 52-55 all depend directly or indirectly from claim 44, and thus include all the elements of distinguished claim 44. Accordingly, applicants respectfully request the withdrawal of the rejection of claims 44, 47, 48, and 52-55 in view of the Petitte Patents. Claim 55 has been canceled, and thus the rejection is believed to be moot as to this claim. Applicants respectfully request a Notice of Allowance for claims 44, 47, 48, and 52-54.

VII. Response to the Rejection under 35 U.S.C. § 103(a)

Claims 44, 47, 48, and 51-57 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are obvious over the '569 Patent in view of Chang 1995. After careful consideration of the rejection and the Patent Office's bases therefor, applicants respectfully traverse the rejection and submit the following remarks.

Applicants respectfully direct the Patent Office's attention to the comments presented hereinabove with respect to Chang 1995. Particularly, applicants respectfully submit that Chang 1995 does not disclose PGC-derived cells that form one or more colonies of tightly packed undifferentiated avian cells that are smaller than primordial germ cells as recited in claim 44.

Additionally, applicants respectfully submit that this deficiency is not cured by the '569 Patent, which also discloses a long-term culture system for PGCs. Thus, neither reference individually, nor the combination of references, discloses or suggests a sustained culture as claimed in claim 44 because there is no disclosure of PGC-derived cells that form one or more colonies of tightly packed undifferentiated chicken cells that are smaller than primordial germ cells.

Applicants respectfully submit that all of the Patent Office's assertions with regard to the instant rejection appear to be based on the contention that the undifferentiated chicken cells claimed in the instant application are PGCs, or alternatively, that the claimed cells are not patentably distinct from PGCs. Applicants respectfully submit that neither of these two assertions is accurate. First, the claimed cultures comprise derivatives of PGCs. This is clearly pointed out in claim 44, which recites that the one or more colonies comprise tightly packed undifferentiated chicken cells that are smaller than primordial germ cells.

Turning first to the disclosure of the '569 Patent, applicants respectfully submit that it is clear that the '569 Patent teaches a method of long term culturing of PGCs in a feeder-free culture with the addition of exogenous growth factors including LIF, bFGF, IGF, and SCF (see col. 5, lines 20-50). Applicants respectfully submit that there is no disclosure in the '569 Patent of any morphological change of the PGCs in the culture to cells that are smaller than PGCs and form tightly packed colonies.

Furthermore, applicants respectfully submit that there is no disclosure in the '569 Patent of making somatic chimeras using PGCs. Rather, the '569 Patent discloses the following:

As discussed, these PGCs can be maintained for long periods in culture with the successful production of chimeric avians. To date, the cells have been maintained in tissue culture for up to about 4 months, with apparently no adverse effects. Also, cells of up to 25 days have been tested for their ability to effectively colonize avian embryonic gonads and produce chimeric birds. However, it is expected that these cells can be cultured indefinitely, with retention of the ability to produce chimeric birds.

Methods for using PGCs to produce chimeras are known in the art as evidenced by the prior art discussed supra. Preferably, PGCs will be transferred into recipient avian embryos according to the methods disclosed in the example while follows. Thereafter, successful chimera production is evaluated based on migration and colonization of PGCs in the gonads, retention of PGC phenotype, or by evaluating for the presence of donor PGCs in gonads after hatching and breeding.

In the present example, the inventors selected genotypes which are easily followed which affect coloration. Donor birds were white broiler type and recipient birds were black feathered birds, respectively, having specific potential genotypes. The putative chimeras were black feathered and produced black/white progeny when mated with black birds. Thereby, successful chimeras were demonstrated based on the production of black/white feathered progeny produced after mating the putative chimeric bird with another black feathered bird.

'569 Patent at column 6, lines 21-48 (emphasis added). Applicants respectfully submit that it is clear from this passage that if chimeras are produced by re-introducing cultured PGCs into an embryo, the chimeras were germline chimeras only. This is shown by the disclosure that all the putative chimeras were black feathered (*i.e.*, no PGC contribution to the feathers in the chimeras) but produced some black/white feathered progeny (*i.e.*, there was PGC contribution to the germline).

Thus, even assuming *arguendo* that the '569 Patent discloses the production of chimeric avians, applicants respectfully submit that it discloses the production of only germline chimeric avians. Applicants respectfully submit that since PGCs differentiate into the germ cells, successful colonization of the gonad by PGCs introduced into an

avian embryo would be expected to produce germline chimeric birds. Again, however, the instantly claimed cultures are not cultures of PGCs, but include cells that are derivatives of PGCs, and as such, the '569 Patent does not support the instant rejection.

Turning now to the disclosure of Chang 1995, applicants respectfully submit that the comments presented hereinabove with respect to the '569 Patent are equally applicable to Chang 1995. The Patent Office's attention is particularly directed to Figure 2 of Chang 1995, which shows PGCs growing in culture. The Figure legend clearly indicates that PGCs grew individually or as aggregates, which applicants respectfully submit are not tightly packed colonies of cells that are smaller than PGCs. See Figure 2(d) of Chang 1995, which shows an aggregate that is considerably different morphologically from the colonies of undifferentiated cells disclosed in the instant application (*compare* Figure 4 of the instant application). With respect to the Patent Office's assertions that PGCs that grew in culture for 4-5 days are colonies of cells as claimed because they are in different wells of a tissue culture plate, applicants respectfully submit that the term "colony" would not be interpreted by the skilled artisan in this manner. Thus, applicants respectfully traverse the Patent Office's proffered characterization of a "colony" of cells.

Accordingly, applicants respectfully submit that the combination of the '569 Patent and Chang 1995 does not support the instant rejection under § 103, and respectfully request that the rejection of claims 44, 47, 48, and 51-57 be withdrawn. Claim 55 has been canceled, and thus the rejection is believed to be moot as to this claim. Applicants respectfully request a Notice of Allowance for claims 44, 47, 48, and 52-54.

VIII. Double Patenting Rejections

VIII.A. Response to the Rejection based on the '740 Patent in view of Chang 1995

Claims 44, 47, 48, and 51-57 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and

8-10 of U.S. Patent No. 5,340,740 (hereinafter "the '740 Patent") in view of Chang 1995.

According to the Patent Office:

Claims 1 and 8-10 claim a sustained culture of undifferentiated avian cells having an ES cell phenotype and methods of making such a culture. '740 did not claim culturing the cells on avian feeder cells or the cell culture made by the method.

However, at the time of filing, Chang taught culturing PGCs on avian stromal cells. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to isolate avian cells having an ES cell phenotype as taught by '740, wherein the avian cells are cultured on avian feeder cells. One of ordinary skill in the art at the time the invention was made would have been motivated to use avian feeder cells to increase the number of PGCs as taught by Chang (abstract).

Official Action at page 16. Applicants have carefully considered the rejection and the Patent Office's bases therefor, and respectfully traverse the rejection as follows.

Applicants respectfully submit that the combination of the '740 Patent and Chang 1995 does not suffice to create a *prima facie* case of obviousness. Particularly, one of ordinary skill in the art would not have believed at the time the instant application was filed that PGCs isolated from the embryonic genital ridge or gonad from an avian embryo at a stage later than stage 14 according to the Hamburger & Hamilton staging system would be capable of forming the colonies of undifferentiated chicken cells that are recited in claim 44. Applicants respectfully direct the Patent Office's attention to page 10, line 22, through page 11, line 2, of the specification, which states:

prior to the disclosure of the present invention, it was the general view among those of ordinary skill in the art that avian embryonic gonadal cells comprising primordial germ cells, such as may be collected from, for example, the avian embryonic genital ridge or gonad, once the embryo had reached a stage associated with gonadal development, were to terminally differentiate to germ cells only.

Thus, applicants respectfully submit that one of ordinary skill in the art at the time in the instant application was filed would have believed that PGCs isolated from the genital ridge or gonad of a later than stage 14 embryo (*i.e.*, an embryo that had reached

a stage associated with gonadal development), were destined for terminal differentiation to germ cells (*i.e.*, were committed to terminal differentiation).

To elaborate, there is no motivation in the cited art to use PGCs isolated from the gonad or genital ridge of later than stage 14 embryos to produce sustained cultures of undifferentiated chicken cells as recited in the instant claims. At the time of filing, one of ordinary skill in the art would have believed that the PGCs located in these regions of an embryo at this stage were committed to terminal differentiation. Thus, contrary to the Patent Office's assertion, the element "isolated from an embryo later than stage 14" does bear patentable weight in the context of an obviousness-type double patenting rejection because such a rejection is based on § 103, and the requisite motivation to combine the references must still be present. Applicants respectfully submit that as with any rejection based on § 103, without a motivation to combine the references as asserted by the Patent Office, a rejection based on § 103 is improper.

Accordingly, applicants respectfully submit that since the skilled artisan believed at the time the instant application was filed that PGCs present within the genital ridge or gonad were committed to terminal differentiation, the skilled artisan would not have been motivated to attempt to produce the instantly claimed cultures from embryos later than stage 14. Applicants respectfully submit that without the required motivation, the instant obviousness-type double patenting rejection is improper, and should be withdrawn.

Turning next to the Patent Office's assertion that "the product (stromal cells and cells having an ES cell phenotype) can be isolated from either a whole stage X embryo or the genital ridge of a stage 15 embryo or by mixing PGCs isolated from Stage X embryos with stromal cells isolated from the germinal ridge of Stage XV embryos" on page 25 of the instant Official Action, applicants respectfully submit the following remarks.

Initially, applicants respectfully submit that according to the EGK staging system (*i.e.*, the staging system that employs Roman numerals), there is no Stage XV. The Abstract of the journal article disclosing the EGK system (Hefzibah Eyal-Giladi and Shimshon Kochav (1976) 49 *Developmental Biology* 321-337) states: "Fourteen

developmental stages preceding Hamburger and Hamilton's stage 2 have been studied from live material and photographed from both upper and lower surfaces" (emphasis added). Thus, applicants respectfully submit that there is no Stage XV in chicken development. There is, however, a Stage 15, but that relates to the Hamburger and Hamilton staging system as used in the instant claims. Thus, Stage XV (if there were such a Stage) and Stage 15 would not be equivalent, so the instant assertion does not support the current rejection.

Continuing with the instant rejection, applicants respectfully traverse the Patent Office's assertion that applicants have argued that the PGCs of Chang were "terminally differentiated" as contended on page 25 of the instant Official Action. Rather, applicants have maintained throughout the instant prosecution that the skilled artisan believed at the time instant application was filed that PGCs present within the gonad or genital ridge of later than stage 14 embryos were committed to terminal differentiation, not terminally differentiated themselves. Given that the skilled artisan would not have believed that committed cells could form colonies of undifferentiated cells, applicants respectfully submit that the skilled artisan would not have believed that PGCs isolated from a chicken "later than stage 14" could form colonies of undifferentiated cells.

And finally, applicants respectfully traverse the Patent Office's assertion that "the claims encompass cultures comprising avian cells having any ES cell phenotype" (Official Action at page 25; emphasis added). Applicants respectfully submit that the phrase "ES cell phenotype" refers to a particular morphology: namely having "a large nucleus, prominent nucleolus, and little cytoplasm". Additionally, applicants have amended claim 44 to further recite that the undifferentiated cells (i) are derived from chicken PGCs isolated from the genital ridge or gonad [of a later than stage 14 embryo], (ii) are smaller than the chicken PGCs [so isolated]; and (iii) form one or more colonies of tightly packed undifferentiated chicken cells expressing an embryonic stem cell phenotype.

Accordingly, applicants respectfully submit that a *prima facie* case of obviousness has not been made out, and as a result, applicants respectfully request that the rejection of claims 44, 47, 48, and 51-57 under the judicially created doctrine of

obviousness-type double patenting as being unpatentable over claims 1 and 8-10 of the '740 Patent in view of the disclosure of the '740 Patent and Chang 1995 be withdrawn. Claim 55 has been canceled, and thus the rejection is believed to be moot as to this claim. Applicants respectfully request a Notice of Allowance for claims 44, 47, 48, and 52-54.

*VIII.B. Response to the Rejection based on the '479 or the '510 Patent
in view of Chang 1995*

Claims 44, 47, 48, and 51-57 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,656,479 or 5,830,510 (hereinafter "the '479 Patent" and "the '510 Patent", respectively) in view of Chang 1995. Applicants have carefully considered the rejection and the Patent Office's bases therefor, and respectfully traverse the rejection as follows.

Applicants initially note that the discussion presented immediately above with regard to the rejection of claims 44, 47, 48, and 51-57 over the '740 Patent in view of the disclosure of the '740 Patent and Chang 1995 is equally applicable to the instant rejection. Summarily, none of the constituent patents that make up the "Petitte Patents" (*i.e.* the '740 Patent, the '479 Patent, and the '510 Patent) disclose the use of PGCs isolated from an avian embryo after stage 14 to produce a culture comprising colonies of undifferentiated chicken cells.

Applicants respectfully submit that the Patent Office's burden is to demonstrate that one of ordinary skill in the art would have been motivated by the teachings of the cited references to create the claimed combination itself. Applicants have contended, and the Patent Office has acknowledged, that those of skill in the art believed that the PGCs used to generate the instantly claimed sustained cultures were believed to be incapable of forming undifferentiated cells expressing an embryonic stem cell phenotype. Thus, the art teaches away from the production of the instantly claimed combination, and thus, there could have been no motivation to employ PGCs isolated from after stage 14.

The Patent Office asserts:

Chang taught culturing PGCs with avian stromal cells isolated from the genital ridge of a stage 27 embryo. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to isolate avian cells having an ES cell phenotype as claimed in '479 and '510 wherein the avian cells are cultured on avian stromal cells isolated from Stage 27 embryos as taught by Chang. One of ordinary skill in the art at the time the invention was made would have been motivated to use stromal cells isolated from stage 27 avian embryos to increase the number of PGCs as taught by Chang.

Official Action at page 26.

Additionally, applicants respectfully submit that as used in the instant application and in the claims the phrase "having an ES cell phenotype" refers to a population of cells that is derived from PGCs, but cannot be "isolated from" a stage 27 embryo as asserted by the Patent Office. As a result, applicants respectfully submit that the Patent Office's assertion that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to isolate avian cells having an ES cell phenotype as claimed in '479 and '510" is inaccurate.

Summarily, applicants respectfully submit that a *prima facie* case of obviousness of claims 44, 47, 48, and 51-57 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of either the '479 Patent or the '510 Patent in view of Chang 1995 has not been presented, and that the instant rejection should be withdrawn. Applicants therefore respectfully submit that claims 44, 47, 48, and 51-57 are in condition for allowance. Claim 55 has been canceled, and thus the rejection is believed to be moot as to this claim. Applicants respectfully request a Notice of Allowance for claims 44, 47, 48, and 52-54.

IX. Discussion of the New Claim

New claim 58 has been added. Support for the new claim can be found throughout the specification of the application as filed, including particularly in the claims as originally filed (see original claims 15, 31, and 43). Additional support for the new claim can be found in Figure 4, particularly Figures 4B-4D.

Applicants respectfully submit that the new claim is patentably distinguished from the cited references for the reasons set forth hereinabove with respect to claim 44. As claim 44 is believed to be distinguished from the cited references and the new claim depends directly from claim 44, applicants respectfully submit that the new claim is also in condition for allowance. Applicants respectfully solicit a Notice of Allowance to that effect.

CONCLUSION

In light of the above Amendments and Remarks it is respectfully submitted that the present application is now in proper condition for allowance, and such action is earnestly solicited.

If any minor issues should remain outstanding after the Examiner has had an opportunity to study the Amendment and Remarks, it is respectfully requested that the Examiner telephone the undersigned attorney so that all such matters may be resolved and the application placed in condition for allowance without the necessity for another Action and/or Amendment.

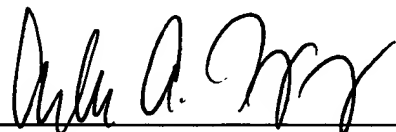
DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this Amendment After Final to Deposit Account No. 50-0426.

Respectfully submitted,

JENKINS, WILSON & TAYLOR, P.A.

Date: 10/04/2005

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